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Searching for new host compounds: synthesis and characterization of novel crown ether-functionalized dendrimers

Dimitrios Alivertis, Vassiliki Theodorou, Georgios Paraskevopoulos and Konstantinos Skobridis*

Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece

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This article is dedicated to the celebration of the 60th birthday anniversary of Professor Edwin Weber, for his great contribution to supramolecular chemistry

Abstract—Novel lipophilic dendrimers as host compounds, that is, **7**–**15**, containing crown ether moieties with different sizes as the core, surrounded by first, second or third generation poly(aromatic ether) wedges, were synthesized by the use of bis(bromomethyl)-substituted crown ethers and Fréchet-type poly(benzyl ether) dendrons as building blocks. The compounds were fully characterized.

Dendrimers are among the most attractive macromolecules, consisting of a multi-functional core and successive branched repeating units extending radially outward. They have attracted a great deal of attention producing various functions in many fields. A particular interest in dendrimer synthesis[1–3] is devoted to the discovery of specific functions and properties that are a direct consequence of the dendritic architecture.[4] The ability of the dendritic shell to encapsulate functional core moieties and to create specific site-isolated nanoenvironments,[4c] and thereby affect molecular properties, has developed the field of host–guest properties of dendritic molecules into a special area of supramolecular chemistry.[5] The combination of dendrimers and other macromolecular topologies as building blocks, is thus an attractive approach to the study of molecular recognition.[6]

Compounds containing crown ethers and dendritic wedges have shown especially interesting ligating properties.[7] Crown ether ligands have been attached to the focal point of light harvesting monodendrons to mimic the energy transduction events in natural photosynthetic systems.[8] Recently, dendritic crowns functionalized with dendritic branching, based on L-lysine repeating units, binding cationic guest species have been described.[9]

Obviously, the cation-binding and extraction ability of crown ethers is critically affected by several factors including the symmetry of the crown ether, the size-fit relationship, the type of the donor atoms, multiplicity, and cooperative effects of neighbouring binding sites. The preorganization of a host molecule towards a certain guest compound is a central determinant of binding power and one of the most important strategies to increase complexing ability and selectivity.[10] Among these, the attachment of an oligo(oxyethylene) chain to a crown ether is perhaps the simplest approach. The introduction of dendritic wedges may thus confer a third dimension to the crown macrocycle, related to the macrobicyclic and macrotricyclic cryptands, which display much stronger complexation towards metallic cations than the conventional crowns.[11]

To the best of our knowledge, all the reports on dendritic crown ethers are concerned with the synthesis and with properties of multi-crown dendrimers and of

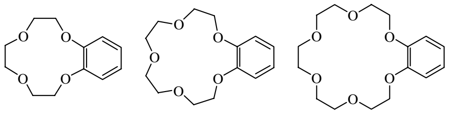

Figure 1. Crown ether building blocks of different sizes as the core.

Keywords: Supramolecular chemistry; Host–guest compounds; Dendrimers; Crown ethers.

* Corresponding author. Tel.: +30 26510 98598; fax: +30 26510 98682; e-mail: kskobrid@cc.uoi.gr

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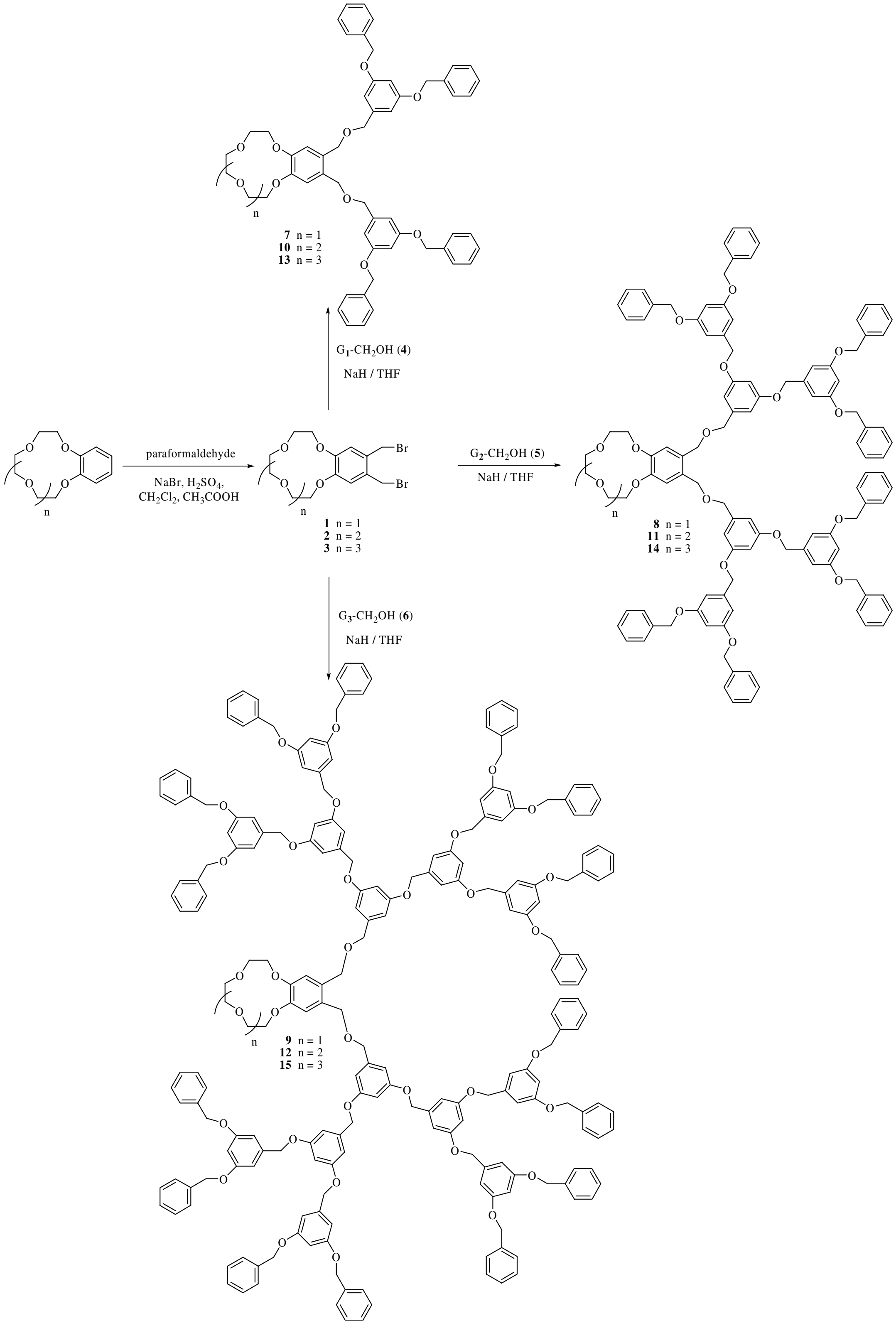
crown ether monodendrons.[7–9,12] In the present study, we report the synthesis and characterization of a series of new crown ether bidendrons. Cation-active crown ether moieties of different sizes, that is, benzo-12-crown-4, benzo-15-crown-5, and benzo-18-crown-6 (Fig. 1), functionalized with dendrons, have been synthesized, in order to illuminate the competition between multiplicity and cooperativity effects. Dendritic branches of Fréchet-type dendrons of the first, second or third generation, which incorporate electron donor



Scheme 1. Formulae and synthesis of crown ether-functionalized dendrimers via a convergent approach.

side-branches moieties with 6, 14 or 30 oxygen atoms, respectively, in their segments, are incorporated proximate to the macrocyclic ring.

The synthetic strategy for the formation of the dendritic crown ethers **7**–**15** involves a reaction between two preformed building blocks: the bifunctional crown ether building block as the core and the poly(benzyl ether) dendron of first, second or third generation as wedges. Treatment of the corresponding branched benzyl alcohol of the first, second or third generation (**4**–**6**) with excess NaH in refluxing THF, followed by the addition of the corresponding bis(bromomethyl)-substituted crown ether (**1**–**3**), afforded compounds **7**–**15** (Scheme 1). The bis(bromomethyl)-substituted benzo-12-crown-4, benzo-15-crown-5 and benzo-18-crown-6 ethers (**1**–**3**) were prepared in one step from the corresponding commercially available crown ethers in nearly quantitative yields, according to published methodology,[13] by bromomethylation with paraformaldehyde, NaBr, H_2SO_4, and acetic acid in dichloromethane. The preparation of the dendritic alcohols **4**–**6** was achieved according to the Fréchet convergent approach.[3a] The progress of the coupling reactions was monitored by thin layer chromatography. The crude reaction products were purified by flash chromatography. All the crown ether-functionalized dendrimers **7**–**15** were monodisperse in pure form. They were unambiguously characterized by IR, ^{1}H and ^{13}C NMR spectroscopies as well as by ESI high resolution mass spectrometry (Supplementary data). The chemical yields were good and decreased with increasing dendrimer generation, as expected. The first generation dendrimers **7**, **10** and **13** and the second generation dendrimers **8**, **11** and **14** were obtained in good yields, ranging between 65–77% and 57–63%, respectively, while the third generation dendrimers **9**, **12** and **15** were obtained in lower yields (37% and 49%).[14]

In their ^{1}H NMR spectra, characteristics of both benzo crown ether functionalities and dendrons could be easily identified. The signals in all the ^{1}H NMR spectra of the crown ether-functionalized dendrimers could be grouped into four regions. The first region included signals with chemical shifts between δ 7.25 and 7.50 ppm, which were due to aromatic protons in the peripheral phenyl rings. The second region showed peaks with chemical shifts at δ 6.50–6.70 ppm, which were due to the aromatic protons between the oxygens and between the oxygens and the benzyl groups in the branches. The third region included signals with chemical shifts between δ 4.40 and 5.00 ppm, which were due to the benzylic protons. In the fourth region, which showed peaks with chemical shifts at δ 3.65–4.20 ppm, the resonances were assigned to the protons of the ethylenic chains of

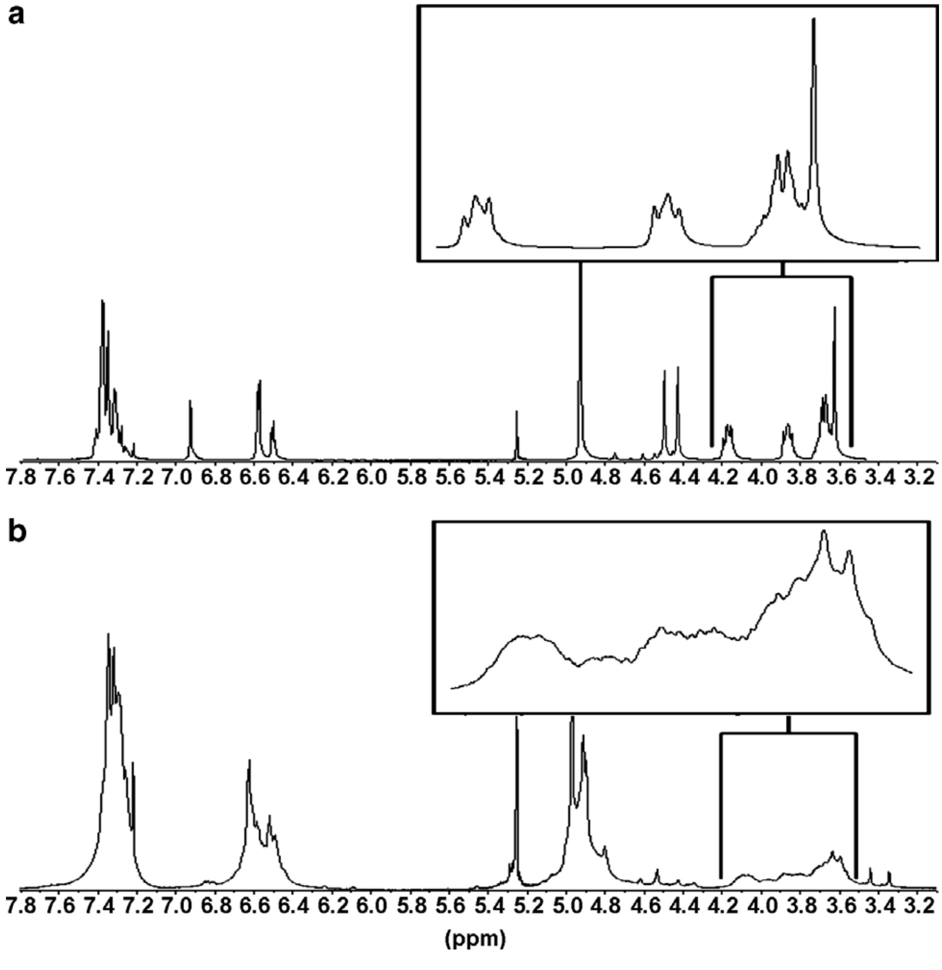


Figure 2. ^{1}H NMR spectra (250 MHz, $CDCl_3$) of the first generation dendrimer **13** (a) and the third generation demdrimer **15** (b).

the crown ether moieties. It was of interest that for the first and second generation dendritic crown ethers **7**–**8**, **10**–**11** and **13**–**14**, respectively, the resonance multiplets corresponding to the methylene protons of the crown ether ring were distinct and well separated. However, in the third generation dendritic crown ethers **9**, **12** and **15** the multiplets, corresponding to the methylene protons were not distinct and appeared more like a broad overlapping singlet, indicating the effect of the third generation dendritic building block on the macrocyclic rings, reducing their conformational flexibility. Figure 2 shows the ^{1}H NMR spectrum of first and third generation dendrimers, **12** and **15**, reflecting the restriction of the flexibility of the crown ether-functionalized dendrimers with increasing dendron generation. In the high resolution electrospray ionization (ESI) mass spectra, the ions were observed as $[M+Na]^+$ as well as, in some cases, doubly charged ions, corresponding to $[M+2Na]^{2+}$ and $[M+2H]^2$. In the high resolution electrospray ionization (ESI) mass spectra, the ions observed as $[M+Na]^+$ as well as, in some cases, as doubly charged ions, corresponding to $[M+2Na]^{2+}$ and $[M+2H]^{2+}$, correlated very well with the calculated molecular masses, thereby supporting the proposed structures.

Most of the compounds (**7**–**12**) were colorless or slightly yellow oils, whilst those containing benzo-18-crown-6 (**13**–**15**) were off-white glassy solids. It is clear that the lipophilicity and rigidity of this class of dendritic crown ethers containing lipophilic dendritic wedges is significantly greater than those of the corresponding simple monocyclic crown ethers. As expected, these compounds were more soluble than the corresponding crown ethers in organic solvents of low polarity, and may serve as a new kind of carrier molecule for transport processes. Moreover, with several of the crown ether-functionalized dendrimers, we observed the formation of very stable inclusion compounds (clathrates) with small molecules. Thus, the compounds could be freed from CH_2Cl_2 only by heating at 50 °C/10^{-3} Torr for several hours.

In summary, a series of novel lipophilic dendritic compounds which contain crown ether moieties of different sizes as the core, surrounded by two poly(aromatic ether) wedges of the first, second or third generation have been synthesized and fully characterized. The host–guest properties, especially the alkali metal compelling abilities and phase transfer catalysis experiments of the new crown ether-functionalized dendrimers, are currently under investigation.

Acknowledgements

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Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR and ESI high resolution mass spectra for compounds **7**–**15**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.014.

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14. *General procedure for the synthesis of the crown ether-functionalized dendrimers* **7**–**15**. To a stirred, gently refluxing, suspension of NaH (120 mg, 5 mmol) in 20 mL of THF was added under argon the corresponding dendritic alcohol of the first, second or third generation (2.2 mmol) in abs. THF (10 mL). After the addition of the dendritic alcohol was complete, the corresponding bis(bromomethyl)-substituted crown ether (1.0 mmol) **4**–**6** in abs. THF (10 mL) was added dropwise. The mixture was heated at reflux for 24–48 h, then allowed to cool to room temperature, quenched carefully with H_2O, and evaporated under reduced pressure. Water was added to the residue and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4), evaporated, and purified by flash chromatography on a silica column. Specific details are given for each compound.

Compound **7**. Eluent: hexane/EtOAc (1:2); yield: 77%; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.74 (s, –OCH_2–, 4H), 3.76–3.80 (m, –OCH_2–, 4H), 4.11–4.15 (m, –OCH_2–, 4H), 4.40 (s, benzylic H, 4H), 4.45 (s, benzylic H, 4H), 4.95 (s, benzylic H, 8H), 6.50 (t, $J = 2.1$ Hz, Ar-H, 2H), 6.56 (d, $J = 2.0$ Hz, Ar-H, 4H) 7.00 (s, Ar-H, 2H), 7.24–7.40 (m, Ar-H, 20H); HRMS (ESI): Calcd for $C_{56}H_{56}O_{10}$ $[M+Na]^+$ *m*/*z* 911.3770, found $[M+Na]^+$ *m*/*z* 911.3764.

Compound **8**. Eluent: hexane/EtOAc (2:3); yield: 57%; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.70 (s, –OCH_2–, 4H), 3.73–3.77 (m, –OCH_2–, 4H), 4.09–4.13 (m, –OCH_2–, 4H), 4.39 (s, benzylic H, 4H), 4.46 (s, benzylic H, 4H), 4.86 (s, benzylic H, 8H), 4.93 (s, benzylic H, 16H), 6.46 (t, $J = 2.2$, Ar-H, 2H), 6.50 (t, $J = 2.2$, Ar-H, 4H), 6.54 (d, $J = 2.1$, Ar-H, 4H), 6.60 (d, $J = 2.2$, Ar-H, 8H), 6.99 (s, Ar-H, 2H), 7.24–7.40 (m, Ar-H, 40H); HRMS (ESI): Calcd for $C_{112}H_{104}O_{18}$ $[M+Na]^+$ *m*/*z* 1759.7120, found $[M+Na]^+$*m*/*z* 1759.7087.

Compound **9**. Eluent: hexane/EtOAc (3:4); yield: 49%; slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.71 (s, –OCH_2–, 4H), 3.74–379 (m, –OCH_2–, 4H), 4.10–4.14 (m, –OCH_2–, 4H), 4.43 (s, benzylic H, 4H), 4.49 (s, benzylic H, 4H), ∼4.78–5.02 (benzylic H, 56H), 6.50–6.70 (m, Ar-H, 42H), 7.03 (s, Ar-H, 2H), 7.25–7.50 (m, Ar-H, 80H); HRMS (ESI): Calcd for $C_{224}H_{200}O_{34}$ $[M+2Na]^{2+}$ *m*/*z* 1739.6858, found $[M+2Na]^{2+}$ *m*/*z* 1739.6853.

Compound **10**. Eluent: EtOAc/CH_2Cl_2/MeOH (2:2:1); yield: 74%; off-white powder; mp 110–112 °C ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.74 (s, –OCH_2–, 8H), 3.85–3.89 (m, –OCH_2–, 4H), 4.12–4.15 (m, –OCH_2–, 4H), 4.44 (s, benzylic H, 4H), 4.51 (s, benzylic H, 4H), 4.99 (s, benzylic H, 8H), 6.55 (t, $J = 2.1$ Hz, Ar-H, 2H), 6.61 (d, $J = 2.1$ Hz, Ar-H, 4H), 6.95 (s, Ar-H, 2H), 7.25–7.42 (m, Ar-H, 20H); HRMS (ESI): Calcd for $C_{58}H_{60}O_{11}$ $[M+Na]^+$ *m*/*z* 955.4033, found $[M+Na]^+$ *m*/*z* 955.4030.

Compound **11**. Eluent: EtOAc/CH_2Cl_2/MeOH (3:3:1); yield: 63%; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.71 (s, –OCH_2–, 8H), 3.82–3.86 (m, –OCH_2–, 4H), 4.09–4.13 (m, –OCH_2–, 4H), 4.43 (s, benzylic H, 4H), 4.51 (s, benzylic H, 4H), 4.90 (s, benzylic H, 8H), 4.97 (s, benzylic H, 16H), 6.51 (t, $J = 2.1$, Ar-H, 2H), 6.54 (t, $J = 2.1$, Ar-H, 4H), 6.59 (d, $J = 2.1$, Ar-H, 4H), 6.65 (d, $J = 2.1$, Ar-H, 8H), 6.94 (s, Ar-H, 2H), 7.24–7.42 (m, Ar-H, 40H); HRMS (ESI): Calcd for $C_{114}H_{108}O_{19}$ $[M+Na]^+$ *m*/*z* 1803.7382, found $[M+Na]^+$ *m*/*z* 1803.7355.

Compound **12**. Eluent: CH_2Cl_2/MeOH (20:1); yield: 37%; slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.71 (s, –OCH_2–, 8H), 3.80–3.87 (m, –OCH_2–, 4H), 4.08–4.14 (m, –OCH_2–, 4H), 4.44 (s, benzylic H, 4H), 4.52 (s, benzylic H, 4H), 4.89 (benzylic H, 24H), 4.97 (s, benzylic H, 32H), 6.50–6.70 (m, Ar-H, 42H), 6.96 (s, Ar-H, 2H), 7.24–7.44 (m, Ar-H, 80H); HRMS (ESI): Calcd for $C_{226}H_{204}O_{35}$ $[M+2Na]^{2+}$ *m*/*z* 1761.6989, found $[M+2Na]^{2+}$ *m*/*z* 1761.6983.

Compound **13**. Eluent: CH_2Cl_2/MeOH (6:1); yield: 65%; off-white powder; mp 66–67 °C ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.65 (s, –OCH_2–, 4H), ∼3.66–3.76 (overlapped m, –OCH_2–, 8H), 3.84–3.88 (m, –OCH_2–, 4H), 4.12–4.16 (m, –OCH_2–, 4H), 4.40 (s, benzylic H, 4H), 4.48 (s, benzylic H, 4H), 4.96 (s, benzylic H, 8H), 6.51 (t, $J = 2.1$ Hz, Ar-H, 2H), 6.58 (d, $J = 2.1$ Hz, Ar-H, 4H) 6.93 (s, Ar-H, 2H), 7.24–7.40 (m, Ar-H, 20H); HRMS (ESI): Calcd for $C_{60}H_{64}O_{12}$ $[M+Na]^+$ *m*/*z* 999.4290, found $[M+Na]^+$ *m*/*z* 999.4299.

Compound **14**. Eluent: CH_2Cl_2/MeOH (8:1); yield: 61%; off-white powder; mp 122–124 °C ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.68 (s, –OCH_2–, 4H), ∼3.70–3.78 (m, –OCH_2–, 8H), 3.88–3.92 (m, –OCH_2–, 4H), 4.15–4.19 (m, –OCH_2–, 4H), 4.46 (s, benzylic H, 4H), 4.55 (s, benzylic H, 4H), 4.93 (s, benzylic H, 8H), 4.99 (s, benzylic H, 16H), ∼6.54–6.60 (two overlapped multiplets, Ar-H, 6H), 6.63 (d, $J = 2.1$ Hz, Ar-H, 4H), 6.69 (d, $J = 2.1$ Hz, Ar-H, 8H); 6.99 (s, Ar-H, 2H), 7.26–7.44 (m, Ar-H, 40H); HRMS (ESI): Calcd for $C_{116}H_{112}O_{20}$ $[M+Na]^+$ *m*/*z* 1847.7639, found $[M+Na]^+$ *m*/*z* 1847.7659.

Compound **15**. Eluent: CH_2Cl_2/MeOH (20:1); yield: 41%; off-white powder; mp 158–160 °C ^{1}H NMR (250 MHz, $CDCl_3$): δ ∼3.55–4.20 (overlapped broad multiplets, –OCH_2–, 20H), ∼4.35–4.50 (two broad singlets, benzylic H, 8H), ∼4.70–5.05 (benzylic H, 56H), ∼6.40–6.75 (overlapped multiplets, Ar-H, 42H), 7.20–7.50 (m, Ar-H, 80H); HRMS (ESI): Calcd for $C_{228}H_{208}O_{36}$ $[M+2H]^{2+}$ *m*/*z* 1761.7300, found $[M+2H]^{2+}$ *m*/*z* 1761.7330.